

EXAMINER'S AMENDMENT/COMMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

No authorization for this examiner's amendment was needed as claim 21 depending to later claim 23 was deemed a mere typo (and should have depended to claim 1, as the immediate claims before and after it did). Both Applicant and the Examiner had overlooked this. A message was left for Applicant's Representative on 6/19/11, that should this interpretation be incorrect, a Supplemental Allowance will be processed to that effect.

Additionally, no authorization was needed to cancel withdrawn claims 17-46 as the subject claims were not eligible for rejoinder under *In re Ochiai* (different method of use, no product elected/found allowable to which a method of making or using applied).

IN THE CLAIMS

In claim 21, line 1, the numeral "23" has been deleted, and the numeral --1-- inserted.

Claims 27-46 are cancelled without prejudice (as being drawn to non-elected, withdrawn claims, not eligible for rejoinder under *In re Ochiai*).

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

Following two RCE's, and after full consideration of the Applicant's arguments (over the outstanding 35 USC 112 2nd rejection) and an updated search of the art, the claimed invention was not found to be reasonably taught or suggested by the prior art of record, and Applicant's arguments are found persuasive over the prior art (response of 11/8/10, page 15), repeated below:

In summary, Applicants have shown that the Examiner has not established *a prima facie* case of obviousness because: (1) the references cited by the Examiner do not teach or suggest protein purification via ion exchange chromatography employing different salt gradients during the washing phase, wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough. (2) there is no motivation or suggestion to modify the reference to reach the instant protein purification method because the references do not disclose protein purification via ion exchange chromatography employing different salt gradients during the washing phase, wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough. (3) there is no reasonable expectation of success that a combination of the references would succeed in producing a protein purification method utilizing ion exchange chromatography and increasing salt gradients due to the lack of disclosure of washing steps employing increasing salt gradients during the washing phase, wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough, and (4) the Examiner has based obviousness on improper hindsight. Accordingly, Applicants request that the rejection of Claims 1-25 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Basey *et al.* in view of Grandics *et al.* and further in view of Winge *et al.* be withdrawn.

As was previously noted (10/17/07 response), the issue narrowed on a distinction between linear salt gradients (Grandics *et al.*) v. a non-linear salt gradient (presently claimed invention); which though appearing to the Examiner to present a routine optimization parameter by the skilled artisan, was firmly traversed by Applicant's assertion that better results via a non-linear gradient was not to be expected:

*The challenge of obtaining high yield and high purity in protein purification in ionic exchange chromatography was solved in the present application by applying a non-linear gradient of ionic strength. It was found that the product species was able to be obtained at highest yield and purity levels upon imposing a series of increasingly shallow rates of increase in ionic strength at increasing elution times. This finding, which is far from obvious, is not suggested by Genentech [Basey *et al.*] or Grandics *et al.*, when taken alone or in combination.*

Thus, it could not have been obvious that applying a non-linear gradient would effect the desired high levels of protein yield and purity.

And as noted in the Non-Final Rejection of 12/28/10:

There is no motivation or suggestion to modify the cited references to reach the Applicants' invention.

The Examiner asserts that "varying the type of salt, amount (e.g. increasing OR decreasing concentration)" qualify as "routinely optimizable parameters." (Page 4 of the instant Final Office Action).

Applicants respectfully disagree. As described in the specification, the inventors found that the instantly claimed wash steps, performed in the order and using the parameters recited in the claims, were effective for polypeptide purification, particularly for resolving a desired polypeptide molecule from a contaminant differing only slightly in ionic charge.

As is recognized in ion exchange chromatography, the more similar the charge on the two molecules to be separated (polypeptide vs. contaminant), the more difficult it is to achieve a separation of the two molecules. The experimental examples in the patent application illustrate the use of the claimed methods to substantially reduce the amount of deamidated and other acidic variants in a purification of anti-HER2 antibody, which is a technically challenging separation owing to the very similar properties of the variants compared with the desired antibody polypeptide.

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The advantage that the instant method provides over the prior art is that, **by using a three slope gradient wash, a greater range of resin load densities are possible while maintaining product quality and not sacrificing yield.** The separation also becomes less sensitive to small variations in buffer composition. Washing steps are often employed to remove a contaminant from the column prior to elution, however, the resolution of species that a gradient wash would technically provide would not appear valuable to one skilled in the art since those species will never be collected. Moreover, multi-slope gradients are very complicated to run in a manufacturing environment and it would strike the unfamiliar process developer as pointless to incorporate such a complicated operation into a wash phase that will be discarded. As discussed above, development of the multi-slope gradient used in the instant method was the solution to the problem of achieving a wide resin load density range while maintaining yield and purity.

The achievement of this improvement in the load density range is a significant improvement over the prior art. A complicated series of interactions occur within the ion exchange column during the wash step and acidic variants are essentially just teased off the resin charge groups. At low resin load densities there are a large number of unoccupied resin binding sites that the acidic variants can loosely re-associate with, which means that from one run to the next, as the amount of protein loaded on the column varies, it can take a longer amount of time or require greater conductivity to get the acidic variants off the column. The three slope gradient of the instant method is a novel and non-obvious solution to this problem. Together the multi-slope gradient wash followed by the step elution provides a method to consistently remove acidic variants with a robust, reproducible process that can be effectively automated and scaled up. The prior art taken alone or in combination would not lead a skilled artisan to apply the multi-slope gradient to the wash step as instantly claimed.

Applicants reiterate that the cited art does not offer suggestions or even recognize a need for modification of their respective methods. In the absence of any recognized failure or shortcomings of these cited methods, the Examiner has provided no motivation for a protein research scientist to pursue any modifications, let alone provide a reasoning for selecting the specifically claimed method of the instant application over the multitude of possible salt gradient combinations possible.

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In summary, Applicants have shown that the Examiner has not established a prima facie case of obviousness because: (1) the references cited by the Examiner do not teach or suggest protein purification via ion exchange chromatography employing different salt gradients during the washing phase, **wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough.** (2) there is no motivation or suggestion to modify the reference to reach the instant protein purification method because the references do not disclose protein purification via ion exchange chromatography employing different salt gradients during the washing phase, wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough. (3) there is no reasonable expectation of success that a combination of the references would succeed in producing a protein purification method utilizing ion exchange chromatography and increasing salt gradients due to the lack of disclosure of washing steps employing increasing salt gradients during the washing phase, wherein the washing involves increasing salt concentration until a predetermined protein concentration is measured in the flowthrough, and (4) the Examiner has based obviousness on improper hindsight. Accordingly, Applicants request that the rejection of Claims 1-25 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Basey et al. in view of Grandics et al. and further in view of Winge et al. be withdrawn.

Applicant's arguments are also deemed persuasive over the 112 2nd rejection (Interview 3/11/11), where:

Applicant indicated, regarding the phrase "resin load densities" that "three or four different loads were tested, and tables (end of examples) provide that you can vary the load in a wide range and the purity and the load remain consistent, and still get the desired results". Based on Applicant's indication that this is an art-recognized phrase and that testing was carried out in support thereof, the phrase is no longer held indefinite.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 6/19/2011

/Maury Audet/
Primary Examiner, Art Unit 1654